REMARKS

Claims 35-44 are pending. Claims 1-26 are canceled. Claims 27-34 have been withdrawn. Claims 35-44 are new. Support for new claim 35 can be found in originally filed claim 19 and throughout the specification, *e.g.*, page 19, lines 1-12, page 7, lines 4-10. Support for new claims 36 and 37 can be found in originally filed claim 19 and throughout the specification, *e.g.*, page 56, lines 19-22, pages 19-20, page 29, lines 21-34. Support for new claims 38-43 is found in claims 21-26 as originally filed in this application. Support for new claim 44 can be found throughout the specification, *e.g.*, page 7, lines 4-10 and page 11, lines 29-31. No new matter has been introduced by way of these amendments.

As a preliminary matter, Applicants would like to draw the Examiner's attention to the Supplemental IDS submitted to the Patent and Trademark Office on July 15, 2003, but has not yet been acknowledged. Applicants respectfully request notification that the references cited therein have been considered.

Priority

The Examiner asserts that the applications upon which priority is claimed fail to provide adequate support for claims 2, 6, 13, 15, 16-18 and 25. In reply, Applicants note that claims 2, 6, 13, 15, and 16-18 have been canceled. With regard to claim 25 (now being re-presented as claim 42), Applicants respectfully traverse the assertion and submit that there is sufficient support in 60/090,473 and 09/189,543 to entitle claim 42 to the benefit of the filing date of the former (*i.e.*, June 24, 1998).

Applicants submit that arrays are adequately described in the priority documents. The specification in both the provisional and parent applications teach several array formats including, for example, FACS in a selective decoding system. *See* 60/060,473 at page 29, lines 10-19; 09/189,543 at on page 22, lines 10-34. One of skill in the art would appreciate that the FACS format described in the provisional and parent applications is a liquid array because FACS was understood in the art to be a liquid array at the time of filing. For example, in 1998, Axys Pharmaceuticals and Luminex received a development grant from the National Institute of Standards and Technology (NIST)for their project entitled "Liquid Array Technology

Development." The deadline for submitting a grant proposal was March 18, 1998. *See* NIST website *at* http//www.atp.nist.gov/www/press/98ann.htm (last visited Nov. 3, 2003) (a copy of which is submitted herewith as Appendix A). Axys Pharmaceuticals defined liquid arrays to "consist of synthetic DNA attached to fluorescent color-coded miniature beads (microspheres) suspended in liquid." *Axys Pharmaceuticals Awarded Grant to Develop New DNA Analysis Technology*, BUSINESS WIRE, October 7, 1998, *at* DIALOG, File No. 16, Accession No. 5880858 (a copy of which is submitted herewith as Appendix B). Axys' definition of "liquid array" comports with Applicants' contention and shows that the skilled artisan, prior to the June 24, 1998 priority date, would have understood that FACS is a liquid array. Accordingly, since Applicants teach FACS in the priority documents and have shown that FACS is a liquid array, Applicants respectfully submit that claim 42 finds support in both 60/090,473 and 09/189,543 applications and is thus entitled to the June 24, 1998 filing date.

Response to Rejections

35 U.S.C. § 112, second paragraph

Claims 9, 16, 23, 25 and 26 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Claims 9 and 16 have been canceled rendering the objection moot with respect to those two claims.

Claim 23 (now claim 40) is rejected as being indefinite for the recitation of "IBL". Claim 35, from which claim 40 depends, defines "IBL" to mean an identifier binding ligand. Support for the terms "IBL" and "identifier binding ligand" can be found throughout the specification, *e.g.*, page 19, lines 2-12. Thus, Applicants respectfully request withdrawal of the rejection.

Claim 25 (now claim 42) is rejected because of the alleged indefiniteness of the term "liquid array." In particular, the Examiner contends that Applicants' use of the term "liquid array" contradicts the accepted meaning of "array". Applicants respectfully disagree with the contention that the term "liquid array" is indefinite.

In a §112, second paragraph rejection, the Examiner's focus should be on whether the claim meets the threshold requirements of clarity and precision, not whether more suitable

language or modes of expression are available. *See* M.P.E.P. § 2173.02. As the Examiner has pointed out in the Office Action (Paper No. 10), Applicants are their own lexicographers and can define the invention in whatever terms they choose as long as the meaning of any term used is defined in the specification. The court has held that the specification should be used to interpret claim terms when such terms are defined therein. *See In re Vogel*, 422 F.2d 438, 441 (CCPA 1970). In addition, the Examiner is required to give the broadest reasonable interpretation consistent with the specification when interpreting the claims. *See In re Hyatt*, 211 F.3d 1367, 1372 (Fed. Cir. 2000).

Here, Applicants note that claim 42 is drawn to a liquid array. The Examiner is respectfully directed to the specification wherein "liquid arrays" have been defined as "a collection of beads that are not spatially organized...Assays are carried out in bulk in solution." Specification, page 45 at lines 28-32. Thus, Applicants have adequately defined the term "liquid array" in the specification such that its meaning would be clear one skilled the art.

Furthermore, Applicants submit that a skilled artisan would be familiar with such terminology. Applicants direct the Examiner's attention to the discussion above regarding priority wherein Applicants show that the term "liquid array" was in use before Applicants' priority date. In addition, Applicants provide the following examples to illustrate that the term "liquid array" is known in the art. First, MiraiBio's Luminex™ 100 technology utilizes "liquid array" terminology to similarly describe a collection of beads that are not spatially organized. *See* Miraibio website *at* http://www.miraibio.com/products/cat_liquidarrays/ view_luminex /index.html (last visited Nov. 3, 2003) (a copy of which is submitted herewith as Appendix C). Second, authors in the "Micro Technology with Macro Results" article use the term "liquid array" to describe a collection of beads, not in a fixed array, used in flow analysis. *See* R. Mariella, Jr. et al., *Micro Technology with Macro Results*, OEMAGAZINE, January 2001, at 34, 36, *at* http://oemagazine.com/fromTheMagazine/jan01/Biomems.pdf (last visited Nov. 3, 2003) (a copy of which is submitted herewith as Appendix D). Thus, Applicants use of the term "liquid array," is a term that is recognized by one of skill the art.

Applicants submit that the term "liquid array" complies with 35 U.S.C. § 112, second paragraph. Accordingly, Applicants request the Examiner to withdraw the rejection.

Claim 26 (now claim 43) is rejected as being indefinite for the recitation of "FACS" because the Examiner contends that FACS is an abbreviation the meaning of which may change over time. In response, Applicants have amended the claim to recite the complete term for FACS (*i.e.*, fluorescence-activated cell sorting). Applicants respectfully request the Examiner to withdraw the rejection.

35 U.S.C. §§ 102(b)

Claims 1, 3-5, 7-12 and 14-25 are rejected under 35 U.S.C. § 102(b) as being anticipated by Walt *et al.* (U.S. Patent No. 6,023,540). Applicants note that since claims 1-18 and 20 have been canceled, the Examiner's rejection as to those claims is moot. With respect to claims 19 and 21-25 (now claims 35 and 38-42), Applicants respectfully traverse the rejection.

Walt is directed to an analytic chemistry system wherein, in some embodiments, microspheres carry bioactive agents for binding to target analytes. Each microsphere is encoded with an optical signature. *See* Walt at column 10, lines 61-63. Detection of the optical signature provides an indication of the identity of the bioactive agent.

In contrast, claim 19 (now claim 35), as amended, is directed to a method that includes an array composition of at least two subpopulations of microspheres wherein the microspheres of each subpopulation have a bioactive agent and at least two decoding attributes wherein at least of one of the decoding attributes is an identifier binding ligand (IBL) and the IBL is different from the bioactive agent. The bioactive agents are identified by detection of each of the first and second decoding attributes.

To anticipate a claim under 35 U.S.C. § 102(b), a reference must teach every element of the rejected claim. *See* M.P.E.P. § 2131. Applicants submit that the reference does not teach each and every element of the present claims.

Applicants' claims require a bioactive agent and at least two decoding attributes wherein at least one of the decoding attributes is an IBL and wherein the IBL is different from the bioactive agent. The IBL will specifically bind a corresponding decoder binding ligand (DBL) to facilitate the elucidation of the bioactive agent's identity. Specification, page 19, lines 2-4. Thus,

presence of both the bioactive agent and the IBL that is different from the bioactive agent, distinguishes Applicants' claims from the teachings of the cited reference which teaches bioactive agents on the bead's surface.

In addition, for at least the reasons above, newly added claim 37 is novel in light of Walt. Accordingly, Applicants respectfully request the Examiner to withdraw the rejection of claim 19 (now claim 35) and dependent claims 21-25 (now claims 36-40).

35 U.S.C. §§ 102(e)

Claims 19-21 and 23-26 are rejected under 35 U.S.C. § 102 (e) as being anticipated by Kamb *et al.* (U.S. Patent No. 6,060,240). Applicants note that claim 20 has been canceled rendering the rejection with respect to this claim moot. New claims 35, 38 and 40-43 correspond to claims 19, 21 and 23-26, respectively. Basically, the Examiner's position appears to be that Kamb discloses the elements of the present claims. Applicants respectfully traverse the rejection.

Kamb is directed to a method utilizing beads with capture fragments attached to their surfaces which can select for target nucleic acid sequences. *See* Kamb at column 10, lines 4-11. The target nucleic acids are labeled with a marker, preferably a visual marker, including chromophores, fluorophores and the like. *Id.* at column 17, lines 30-32. The captured targets are sorted based on the particular label used. In Example 2, Kamb discloses the use of FACS to sort between two target pools labeled with two different fluorophores. *Id.* at column 31, lines 25-27.

As noted previously, claim 19 (now claim 35) is directed to a method that includes providing an array composition comprising at least two subpopulations of microspheres, the microspheres of each subpopulation comprising a bioactive agent and at least two decoding attributes wherein at least one of said decoding attributes is an IBL that is different from the bioactive agent. The bioactive agents are identified by detection of each of the first and second decoding attributes.

As noted above, 35 U.S.C. § 102 requires the cited reference to teach each and every element of the claim in order to anticipate the claim. Here, Applicants respectfully submit that Kamb fails to teach each and every element of the claims.

Kamb only teaches the presence of a bioactive agent on beads. However, Kamb does not teach the presence of at least two decoding attributes, wherein at least one of the decoding attributes is an IBL that is different from the bioactive agent as claimed. Absent a teaching of *both* a bioactive agent *and* at least two decoding attributes wherein at least one of said decoding attributes is an IBL that is different from the bioactive agent, Kamb does not anticipate claim 35.

Moreover, Kamb also does not teach the detection of each of the first and second decoding attributes to identify each of the bioactive agents. Rather, Kamb discloses beads with capture fragments attached to their surfaces and sorting of the beads by FACS detection of labeled target bound to the capture fragments. Kamb at column 10, lines 4-11. Kamb then requires a subsequent decoding step using PCR, gas chromatography, etc. to identify the bound target *Id.* at column 21, line 25 to column 22, line 57. Thus, Kamb describes a system of detection that requires only detection of the single bound target on each bead to obtain satisfactory results. There is no teaching or suggestion in Kamb of detecting two decoding attributes in addition to detecting the bound target.

In addition, for at least the reasons above, newly added claim 37 is novel in light of Kamb. Because Kamb does not teach all the elements disclosed in the claimed invention, Applicants respectfully request the Examiner to withdraw the rejection of claim 19 (now claim 35) and dependent claims 21 and 23-26 (corresponding to current claims 38 and 40-43, respectively).

35 U.S.C. § 103

Claims 2-6 and 13 are rejected under 35 U.S.C. § 103 as being unpatentable over Walt *et al.* (6,023,540) in view of Brenner *et al.* (U.S. Patent No. 5,863,722). Applicants note that these claims have been canceled rendering the rejection moot.

Claim 26 is rejected under 35 U.S.C. § 103 as being unpatentable over Walt *et al.* (6,023,540) in view of Kamb *et al.* (6,060,240). In particular, the Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the FACS detection of Kamb to the detection of Walt to thereby detect bioactive agents

using FACS for the expected benefits of very rapid and accurate detection as taught by Kamb. Applicants respectfully traverse the rejection.

Initially, Applicants note that claim 26 has been canceled. However, new claim 43 includes language similar to originally filed claim 26 so the rejection will be addressed referring to currently submitted claim 43. Claim 43 is drawn to a method that includes providing a liquid array composition comprising a at least two subpopulations of microspheres, wherein the microspheres of each subpopulation comprises a bioactive agent and at two decoding attributes wherein at least one of the decoding attributes is an IBL and the IBL is different from the bioactive agent. The bioactive agents are identified by FACS detection of each of the first and second decoding attributes.

As the Examiner is aware, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Applicants submit that not all claim elements are present in Walt, Kamb, or the combination of the two. As discussed above regarding the rejections under U.S.C. §§ 102(b) and 102(e), neither the passages cited in Walt or Kamb describe both a bioactive agent and at least two decoding attributes wherein at least one of said decoding attributes is an IBL that is different from the bioactive agent nor the identification of the bioactive agent by detecting at least a first and a second decoding attribute wherein at least one of the decoding attributes is an IBL and that the IBL is different from the bioactive agent. Again, the passages cites for Walt describes detection/decoding via optical signatures rather than using at least a first and a second decoding attribute wherein at least one of said decoding attributes is an IBL that is different from the bioactive agent. And Kamb does not cure the deficiencies of Walt because Kamb teaches FACS detection of bound target and subsequent decoding of the target using methods such as PCR or

gas chromatography rather than detection and decoding via at least two decoding attributes wherein at least one decoding attribute is an IBL that is different from the bioactive agent. Accordingly, Applicants submit that the cited references taken alone or in combination, fail to teach or suggest each element of the claims.

In addition, Applicants maintain that even assuming, *arguendo*, that all of the elements of the claimed invention were taught or suggested by the combination of references, one of ordinary skill in the art would not have been motivated to combine the references. To show the requisite motivation, the Examiner must point to specific teachings in the cited references as to a teaching or suggestion to combine the reference. Here, the Examiner states that the skilled artisan would be motivated to use the benefits of very rapid and accurate detection as taught by Kamb to detect the bioactive agents of Walt. While Kamb discusses benefits of FACS analysis, there is no specific teaching that would have motivated the skilled artisan to discard the methods of Walt, which are also described as rapid and accurate, and replace them with the methods of Kamb. The mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *See In re Mills*, 916 F.2d 680 (Fed. Cir. 1990). There is no suggestion in either reference of modifying or combining the references to reach the claims of the present invention.

Furthermore, if the proposed modification or combination of the prior art would change the principle operation of the prior art being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *See In re Ratti*, 270 F.2d 810 (CCPA 1959). Here, Applicants submit that combining the two references would change the principle operation of Walt. Walt is directed to a random array which allows for simultaneous detection of thousands of beads based on fixed coordinates in an array. In contrast, Kamb is directed to a FACS method in which the beads are detected sequentially based on time of passage in a fluid stream. There is no suggestion in the art of record that a fixed array of Walt can be detected in a FACS instrument or in any fluid stream using the methods of Kamb. Thus, the principal operation of Walt would have to be changed in order to combine the methods of Kamb.

Moreover, there is no teaching in the references taken alone or in combination that FACS analysis is faster or more accurate than the fiber optic bead array of Walt. Quite the

contrary, Kamb seems to suggest that there are limits to the FACS detection method. For example, Kamb states that, "[a] FACS machine cannot detect the signal from fewer than 1,000-10,000 fluorophores. Thus, the reaction must proceed sufficiently towards completion such that this minimum number of target fluorophores becomes annealed to the correct bead." Kamb at column 20, line 65 to column 21, line 2. There is no reason, then, why a person skilled in the art would choose to modify the simultaneous detection and decoding method of Walt to the serial bead detection method of Kamb which still requires additional steps to decode the signal. Thus, there is no requisite motivation from either references alone or in combination to detect Walt's beads using FACS as taught by Kamb.

Accordingly, because not all claim elements are present in the cited references and because there is inadequate motivation for the combination of the references, Applicants submit that the rejection is improper. Applicants respectfully request the Examiner to withdraw the rejection.

Double Patenting

Claims 1, 3-5 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 6, 12 and 13 of U.S. Patent No. 6,429,027. Applicants note that claims 1, 3-5 have been canceled rendering the rejection moot.

Claims 1-7, 15-22 and 24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 15-36 of copending Application No. 09/189,543. Applicants note that claims 1-7 and 15-18 have been canceled rendering the rejection moot at to those claims.

With regard to claims 19-22 and 24 (now claims 35, 38, 39, and 41, respectively), Applicants will consider filing a terminal disclaimer if it is necessary and appropriate at the time there is an indication of otherwise allowable subject matter.

Claims 8-14 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting a being unpatentable over claims 8-14, 16-28 and 30-35 of copending Application No. 09/344,526. Applicants note that claims 8-14 have been canceled rendering the rejection moot.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and early notification to this effect is solicited. The Examiner is invited to contact the undersigned at (415) 781-1989 if any issues remain.

Respectfully submitted,
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